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PATENT & TRADEMARK OFFICE

PATENT APPLICATION

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

Applicants:	Anthony et al.			
Serial No.:	09/973,853	Case No.: 20757Y		Art Unit: 1624
Filed:	October 10, 2001			Examiner: Coleman, Brenda Libby
For:	AZA- AND POLYAZA-NAPHTHALENYL CARBOXAMIDES USEFUL AS HIV INTEGRASE INHIBITORS			

Commissioner for Patents
P.O. Box 1450
Alexandria, VA 22313-1450

DECLARATION OF DARIA J. HAZUDA UNDER 37 C.F.R. § 1.132

Sir:

I, Daria J. Hazuda, hereby declare and say:

1. I am a citizen of the United States, and I reside at 4612 Frost Lane, Doylestown PA 18901.

2. I graduated in 1986 from the State University of New York located in Stony Brook, NY with a Ph.D. in biochemistry.

3. I have been employed since 1989 by Merck & Co. and am currently located in West Point, Pennsylvania, where I am Executive Director of Biological Chemistry. Since 1998 I have been director of the antiviral research programs at Merck. I have been the project leader of the HIV-1 integrase program since its inception in 1994.

4. I attach a copy of my resumè as Exhibit 1, which provides further information on my educational background and work experience and includes a list of my publications, abstracts, invited presentations and patents.

5. I have reviewed and understand the contents of U.S. application serial no. 09/973,853 (hereinafter referred to as the "subject application"). The subject application describes and claims certain 8-hydroxy-1,6-naphthyridine-7-carboxamides (hereinafter alternatively referred to as "naphthyridine compounds") and their pharmaceutically acceptable salts, pharmaceutical compositions comprising a therapeutically effective amount of one of the naphthyridine compounds and a pharmaceutically acceptable carrier, and methods of treating HIV infection and of treating or delaying the onset of AIDS in a subject in need of such treatment by administration of one of the naphthyridine compounds to the subject.

6. I have also read and understand the Office Action mailed April 1, 2004 concerning the subject application ("Office Action"), and I have read and understand the following documents, both of which were cited in the Office Action:

D1. Yves Pommier et al., "Retroviral integrase inhibitors year 2000: update and perspectives", *Antiviral Research* 2000, 47: 139-148. ("Pommier et al.")

D2. Erik De Clercq, "New Anti-HIV Agents and Targets", *Medicinal Research Reviews* 2002, 22 (6): 531-565. ("De Clercq")

7. In the Office Action, the Examiner rejected the claims directed to pharmaceutical compositions and to methods of treatment as described in Paragraph 5 above as not being enabled. The Examiner questioned whether the mode of action of the naphthyridine compounds is inhibition of the integrase enzyme and indicated that the use of the naphthyridine compounds for treating HIV infection and AIDS is a general idea that may or may not be workable. More particularly, the Examiner asserted that:

> HIV integrase inhibitors may not necessarily be the mode of action of the compounds, which are tested. Pommier et al., Antiviral Research exhibits many compounds which are suspected of being HIV-1 integrase inhibitors in Table 4 on page 145. However, is integrase really the target. As pointed out by Pommier, diketo acids are the only compounds found to selectively target integrases. Erik De Clercq also stated in 2002 that "the problem with integrase inhibitors is that while they might be effective in an enzyme-based assay, their anti-HIV activity in cell culture may be masked by cytotoxicity, and if they do exhibit anti-HIV activity, this could, at least in some cases be attributed to antiviral actions targeted at other steps in the HIV replicative cycle."
>
> ...
>
> Patent Protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable. Tossing out the mere germ of an idea does not constitute enabling

disclosure. Genetech Inc. v. Novo Nordisk 42 USPQ2d 1001. (from the paragraph bridging pages 2 and 3 of the Office Action)

I present below data and remarks addressing the issues raised by the Examiner.

8. I directed studies to characterize the HIV antiviral activity and mode of action of a naphthyridine compound identified as L-870,810 (which corresponds to the compound of Example 152 in the subject application). These studies compared L-870,810's mode of action with that of diketo acid HIV integrase inhibitors. This study and its results are described in a manuscript (hereinafter referred to as "M1") that has been submitted for publication in the *Proceedings of the National Academy of Sciences*. A copy of M1 is attached as Exhibit 2 and the disclosure of M1 is incorporated herein by reference in its entirety. Paragraphs 9 - 12 below are based on the experiments and results set forth in M1.

9. Like the diketo acids, L-870,810 is a selective inhibitor of HIV-1 integrase mediated strand transfer. When assayed using purified recombinant HIV-1 integrase (see page 4 of M1 for a description of the assay), L-870,810 inhibits strand transfer with apparent IC_{50}'s of 8 and 15 nM using 0.5 nM and 5 nM target DNA, respectively. L-870,810 exhibits reduced activity with respect to assembly and 3' end processing (IC_{50}'s of 85 and 250 nM in 0.5 and 5 nM target DNA). The preferential inhibition of strand transfer and the sensitivity of L-870,810 to the concentration of target substrate are consistent with previous studies (see reference 7 in M1) that suggest that these inhibitors are mechanistically indistinguishable from the diketo acids and bind to the target DNA site of the integration complex. In competitive binding experiments (see page 5 of M1), L-870,810 displaces radiolabeled L-731,988 (an exemplary diketo acid HIV-1 integrase inhibitor - compound **1** in Figure 1 of M1) from the integrase donor complex with a K_i of 3 nM indicating that these inhibitors bind to the assembled DNA complex within the same or overlapping regions of the active site.

10. The mechanism of action of L-870,810 on HIV-1 replication has been evaluated by assessing DNA synthesis and integration in infected cells using quantitative PCR (see pages 5-6 of M1 for a description of the methods). SupT1 cells were acutely infected by co-culturing the cells with the HIV-1 chronic producer Molt-IIIB cells in the presence or absence of L-870,810, the diketo-acid L-731,988, and the non-nucleoside reverse transcriptase inhibitor ("nnRTI"), L-697,661 (described in ref. 23 of M1). HIV-1 specific products were quantified and normalized relative to mitochondrial DNA. Neither L-870,810 nor the diketo-acid affects reverse transcription at concentrations ten-fold greater than that required to inhibit replication. In

contrast, both L-870,810 and the diketo-acid reduce the integrated HIV-1 DNA to undetectable levels and increase 2-LTR circles; at 24 hours post infection, a 5.9 fold increase in 2-LTR circles was observed with L-870,810 (see Figure 3 of M1). Neither integrated HIV-1 DNA or unintegrated 2-LTR circle DNAs were detected in the presence of the nnRTI. As shown for the diketo acids, the absence of integration products and the accumulation of 2-LTR circles provide evidence that the antiviral activity of L-870,810 is a direct consequence of its effect on integration.

11. Serial passage of HIV-1 in cell culture in the presence of L-870,810 selects for viruses that exhibit reduced susceptibility to the inhibitor and accumulate mutations in integrase. Population sequencing of the integrase coding region in multiple clones intermittently during selection with L-870,810 identified mutations that were acquired sequentially over several months: F121Y/T125K (six months), V72I/F121Y/T125K and V72I/F121Y/T125K/V151I (3/8 and 5/8 clones, respectively after 9 months). The L-870,810 mutations were found to map within the integrase active site. As may be seen by reference to Table 1 of M1, viruses containing the integrase mutations selected by L-870,810 were four to 100-fold less sensitive to the inhibitor and resistance was enhanced with the addition of those mutations accumulated during selection.

12. The antiviral activity of L-870,810 has been profiled in viral replication assays (see page 5 of M1) using different cell types and a variety of M- and T-tropic isolates of HIV-1. In the presence of 10% fetal bovine serum or 50% normal human serum, the compound inhibits the replication of the laboratory adapted HIV-1 isolate H9/IIIB in MT-4 T lymphoid cells with mean CIC_{95}'s of 15 nM and 100 nM, respectively. L-870,810 also inhibits HIV-1 clinical isolates and exhibits comparable activity against non-syncytia ("NSI") and syncytia ("SI") viruses from clades A, B, C, D and F. As expected for a compound with a novel mechanism (integrase inhibition), L-870,810 is active against multi-drug resistant viruses such as MDRC4 (IC_{50}'s of 4 nM), which has multiple mutations in reverse transcriptase and protease and exhibits 5 fold or greater resistance to most nucleoside reverse transcriptase inhibitors ("nRTIs"), nnRTIs, and protease inhibitors ("PIs") (N. Parkin, personal communication).

13. The results described in Paragraphs 9-12 (e.g., potent activity in strand transfer assays, potent activity in replication assays, competitive binding with diketo acid, effectiveness in inhibiting HIV replication in viruses resistant to nRTIs and nnRTIs and PIs, lack of inhibition of reverse transcription in combination with an absence of integration products and the accumulation of 2-LTR circles, and selection for integrase mutants) show that L-870,810 is a potent inhibitor of HIV replication whose mechanism of action is inhibition of integrase. The

results further show that L-870,810 inhibits HIV infection by a mechanism that is indistinguishable from that of the diketo acids, which, as acknowledged in the Office Action, are known to selectively target integrase. Still further, the sequencing results have identified specific mutations in integrase that engender HIV with resistance to L-870,810, thereby validating integrase as the target responsible for the antiviral effect.

14. I directed a study of the efficacy of L-870,812 (which corresponds to the compound of Example 136 in the subject application) *in vivo* against simian-human immunodeficiency virus ("SHIV"), which is closely related to HIV-1, by administration of L-870,812 to SHIV-infected rhesus macaques. This study and its results are described in a manuscript (hereinafter referred to as "M2") that has been submitted for publication in *Science.* A copy of M2 is attached as Exhibit 3 and the disclosure of M2 is incorporated herein by reference in its entirety. Paragraphs 15 - 17 below are based on the experiments and results reported in M2.

15. In the L-870,812 *in vivo* study, two infected cohorts with six animals each were employed. In one cohort, the animals started therapy (oral administration twice per day of 10 mg/kg) prior to virus-mediated CD4 cell depletion and near the peak of acute viremia at day 10 and were continued on therapy until day 87. In the other cohort, therapy was delayed until the chronic phase was well established at day 87, after which therapy continued for 45 days. Plasma viral RNA and CD4 cell counts were monitored in all animals twice weekly. Antiviral cellular immune responses were also evaluated by a variety of other techniques (see bottom of page 2 of M2), and resistance was also assessed by sequencing the integrase coding region from plasma vRNA for each treated animal at every time point with detectable viral load.

16. In the early treatment cohort, in the untreated animals (i.e., prior to day 10) the integrase sequence determined at each time point was identical to that of the original challenge virus, whereas a mutation in integrase at position 155 (N to H) was observed beginning on days 28 and 32 in two of the treated animals with detectable viremia. In the delayed treatment cohort, by day 112 (i.e., 25 days after initiating therapy) animals that experienced incomplete suppression selected virus expressing the N155H mutation in integrase. The selection of a resistance mutation *in vivo* that maps to integrase is strong evidence that the mode of action of L-870,812 is integrase inhibition.

17. As may be seen by reference to Figure 2 of M2, the early treatment cohort exhibited either a minimal or a transient decrease in circulating CD4 cell count which recovered

and stabilized within ten days after initiating therapy. The animals maintained a CD4 cell count above 200 cells/μL for the entire treatment period, and in 4 of the 6 animals viral replication was suppressed to undetectable levels. As shown in Figure 3 of M2, L-870,812 therapy in the delayed treatment cohort was initially effective, although, compared to the early treatment group, was less effective over time. This antiviral activity of L-870,812, when administered as monotherapy, demonstrates the *in vivo* biological activity of integrase inhibitors and demonstrates that such compounds can be engineered with the appropriate potency and pharmacokinetic properties necessary to achieve efficacy in HIV-1 infected subjects.

18. The results described above for L-870,810 and L-870,812 demonstrate that the 8-hydroxy-1,6-naphthyridine-7-carboxamide compounds claimed in the subject application (i) are *in vitro* and *in vivo* inhibitors of HIV replication whose mode of action is inhibition of integrase and (ii) are useful for inhibiting integrase, treating HIV infection, delaying the onset of AIDS, and treating AIDS in subjects in need thereof.

19. I hereby declare that all statements made herein of my own knowledge are true and all statements made on information and belief are believed to be true; and further that these statements are made with knowledge that willful false statements and the like so made are punishable by fine or imprisonment or both under 18 U.S.C. § 1001, and that such willful false statements may jeopardize the validity of the subject application or any patent issuing therefrom.

April 29, 2004
Date

Daria J. Hazuda
Daria J. Hazuda

CURRICULUM VITAE

Daria Jean Hazuda, Ph.D.

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I. EDUCATION

School	Date	Major	Degree
Rutgers University New Brunswick, NJ	**1981**	**Biomathematics**	**B.A. Magna Cum Laude**

Thesis: Chromasomal Plasticity-Evolution of the D-Ribose Operon
Advisor: Dr. Morad Abou-Sabe', Department of Microbiology

School	Date	Major	Degree
State University of New York Stony Brook, NY	**1986**	**Biochemistry**	**Ph.D.**

Thesis: Structural and Functional Studies on Transcription Factor IIIA
Advisor: Dr. Cheng-Wen Wu, Department of Pharmacology

II. EMPLOYMENT HISTORY

6/2001 - present	Executive Director, Department of Biological Chemistry, Merck Research Laboratories, West Point, PA
3/2000-6/2001	Senior Director, Department of Antiviral Research, Merck Research Laboratories, West Point, PA
11/1998-3/2000	Director, Department of Antiviral Research Merck Research Laboratories, West Point, PA
1996-1998	Sr. Research Fellow, Department of Antiviral Research Merck Research Laboratories, West Point, PA
1994-1996	Research Fellow, Department of Antiviral Research Merck Research Laboratories, West Point, PA

II. EMPLOYMENT HISTORY (Continued)

1989-1994	Sr. Research Biochemist, Department of Virus & Cell Biology Merck Research Laboratories, West Point, PA
1986-1989	Postdoctoral Fellow, Department of Molecular Genetics Smith, Kline and French, Swedeland, PA
1983-1986	Graduate Research Assistant, Department of Biochemistry State University of New York, Stony Brook, NY
1981-1983	Graduate Teaching Assistant, Department of Biochemistry State University of New York, Stony Brook, NY

III. EXTRAMURAL ACTIVITIES

1. Ad hoc member of NIH AAR1 and California UARP study sections (1997-2001)
   Reviewer: NIH AAR3 (2001-present)
   Developmental Therapeutics Program Aids Review Group (1999)
   Office of Aids Research (OAR) Review Committee (2000)
   AMFAR, New Viral Targets Think Tank (2000, 2002)
   Adult AIDS Clinical Trials Group Review Committee (2003)

2. Ad hoc reviewer for J. Virol, J. Biol. Chem, Biochemistry, Protein Science, Antimicrob. Agents Chemother., AIDS Research and Human Retroviruses, Drug Design and Development, Proc. Natl. Acad. Sci., and Nature and Medicine

3. Scientific Committee International HIV Drug Resistance Workshop (2003 and 2004)

IV. SOCIETY MEMBERSHIPS

American Society for Biochemistry and Molecular Biology
The Protein Society
American Society for Microbiology
American Society of Neuroscience

V. ACADEMIC/PROFESSIONAL HONORS

Sigma XI
Phi Beta Kappa
NIH Predoctoral Fellowship
Highest Distinction 1981, Department of Microbiology, Rutgers University
Henry Rutgers Scholar

VI. PUBLICATIONS

1. Abou-Sabe, M., Pilla, J., **Hazuda, D.,** and Ninfa, A. (1982). Evolution of the D-ribose operon on Escherichia coli B/r. J Bacteriol 150, 762-769.
2. Hanas, J. S., **Hazuda, D. J.,** Bogenhagen, D. F., Wu, F. Y., and Wu, C. W. (1983). Xenopus transcription factor A requires zinc for binding to the 5 S RNA gene. J Biol Chem 258, 14120-14125.
3. Hanas, J. S., **Hazuda, D. J.,** and Wu, C. W. (1985). Xenopus transcription factor A promotes DNA reassociation. J Biol Chem 260, 13316-13320.
4. **Hazuda, D. J.,** and Wu, C. W. (1986). DNA-activated ATPase activity associated with Xenopus transcription factor A. J Biol Chem 261, 12202-12208.
5. **Hazuda, D. J.,** Lee, J. C., and Young, P. R. (1988). The kinetics of interleukin 1 secretion from activated monocytes. Differences between interleukin 1 alpha and interleukin 1 beta. J Biol Chem 263, 8473-8479.
6. Young, P. R., **Hazuda, D. J.,** and Simon, P. L. (1988). Human interleukin 1 beta is not secreted from hamster fibroblasts when expressed constitutively from a transfected cDNA. J Cell Biol 107, 447-456.
7. Young, P. R., **Hazuda, D. J.,** Connor, J., and Dalton, B. (1988). Transcription and translation of IL1a and IL1ß in the presence of the glucocorticoid hormone dexamethasone, in monokines and other non-lymphocytic cytokines. (Powanda, M., Oppenheim, J. J., Kluger, M. J., and Dinarello, C., eds.). Alan R. Liss, Inc., New York.
8. **Hazuda, D.J.,** Lee, J. C., and Young, P. R. (1988). The secretion kinetics of IL1's α and ß from human monocytes are distinct, in monokines and other non-lymphocytic cytokines. (Powanda, M., Oppenheim, J. J., Kluger, M. J., and Dinarello, C., eds.). Alan R. Liss, Inc., New York.
9. **Hazuda, D.,** Webb, R. L., Simon, P., and Young, P. (1989). Purification and characterization of human recombinant precursor interleukin 1 beta. J Biol Chem 264, 1689-1693.
10. **Hazuda, D. J.,** Strickler, J., Kueppers, F., Simon, P. L., and Young, P. R. (1990). Processing of precursor interleukin 1 beta and inflammatory disease. J Biol Chem 265, 6318-6322.
11. **Hazuda, D. J.,** Perry, H. C., Naylor, A. M., and McClements, W. L. (1991). Characterization of the herpes simplex virus origin binding protein interaction with OriS. J Biol Chem 266, 24621-24626.
12. **Hazuda, D. J.,** Strickler, J., Simon, P., and Young, P. R. (1991). Structure-function mapping of interleukin 1 precursors. Cleavage leads to a conformational change in the mature protein. J Biol Chem 266, 7081-7086.

13. **Hazuda, D. J.,** Perry, H. C., and McClements, W. L. (1992). Cooperative interactions between replication origin-bound molecules of herpes simplex virus origin-binding protein are mediated via the amino terminus of the protein. J Biol Chem 267, 14309-14315.

14. Perry, H. C., **Hazuda, D. J.,** and McClements, W. L. (1993). The DNA binding domain of herpes simplex virus type 1 origin binding protein is a transdominant inhibitor of virus replication. Virology 193, 73-79.

15. **Hazuda, D. J.,** Hastings, J. C., Wolfe, A. L., and Emini, E. A. (1994). A novel assay for the DNA strand-transfer reaction of HIV-1 integrase. Nucleic Acids Res 22, 1121-1122.

16. **Hazuda, D. J.,** Wolfe, A. L., Hastings, J. C., Robbins, H. L., Graham, P. L., LaFemina, R. L., and Emini, E. A. (1994). Viral long terminal repeat substrate binding characteristics of the human immunodeficiency virus type 1 integrase. J Biol Chem 269, 3999-4004.

17. Tomassini, J., Selnick, H., Davies, M. E., Armstrong, M. E., Baldwin, J., Bourgeois, M., Hastings, J., **Hazuda, D.,** Lewis, J., McClements, W., Ponticello, G., Radzilowski, E., Smith, G., Tebben, A., and Wolfe, A. (1994). Inhibition of cap (m7GpppXm)-dependent endonuclease of influenza virus by 4-substituted 2,4-dioxobutanoic acid compounds. Antimicrob Agents Chemother 38, 2827-2837.

18. LaFemina, R. L., Graham, P. L., LeGrow, K., Hastings, J. C., Wolfe, A., Young, S. D., Emini, E. A., and **Hazuda, D. J.** (1995). Inhibition of human immunodeficiency virus integrase by bis-catechols. Antimicrob Agents Chemother 39, 320-324.

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20. Byrnes, V., and **Hazuda, D.** (1996). A system to analyze and identify inhibitors of HIV-1 gene regulation using a defective integrated provirus. Methods Enzymol 275, 348-361.

21. LaFemina, R. L., Bakshi, K., Long, W. J., Pramanik, B., Veloski, C. A., Wolanski, B. S., Marcy, A. I., and **Hazuda, D. J.** (1996). Characterization of a soluble stable human cytomegalovirus protease and inhibition by M-site peptide mimics. J Virol 70, 4819-4824.

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35. Li, Y., Yan, Y., Zugay-Murphy, J., Xu, B., Cole, J. L., Witmer, M., Felock, P., Wolfe, A., **Hazuda, D.,** Sardana, M. K., Chen, Z., Kuo, L., and Sardana, V. (1999). Purification,

solution properties and crystallization of SIV integrase containing a continuous core and C-terminal domain. Acta Crystallogr D Biol Crystallogr 55, 1906-1910.

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VII. ABSTRACTS

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